Nitrofurantoin

CAS #67-20-9
Swiss CD-1 mice, at 0.0, 0.03, 0.06, and 0.12% in feed
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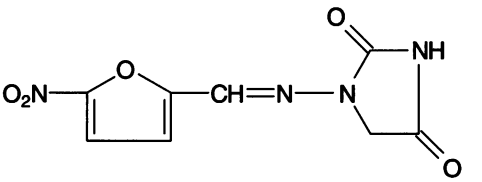

Nitrofurantoin (NF) is used as an antibacterial agent and is one of a group of biologically active nitroaromatic compounds. It was tested for its effects on reproduction and fertility in Swiss CD-1 mice using the RACB protocol because previous studies had reported adverse effects on sperm production and on female reproductive end points, although fertility studies had indicated no adverse effects. This study was performed to address this discrepancy, and also as part of a larger effort by the NTP to generate some public-access information of NF. Data from a 2-week dose-range-finding study (Task 1) were used to set exposure concentrations for the Task 2 continuous cohabitation study at 0.03, 0.06, and 0.12% in feed. Based on mean feed consumption and body weights, estimated daily dosages were approximately 50, 100, and 180 mg/kg/day.

In the F_0 generation, seven mice died: two controls, two low dose, two middle dose, one high dose from causes ranging from septicemia to bacterial metritis. For several animals, the cause of death could not be determined.

During Task 2, there was a 16% reduction in the number of live pups per litter as the high dose, although pup viability or weight were unaffected. Female postpartum body weights were reduced at the high dose by approximately 8%, and in the middle dose group by approximately 5% for the first three litters. Daily feed consumption was reduced only at the high dose, and then only during weeks 14 and 18 (by approximately 15%).

The last litter was reared by the dam until weaning. While NF did not impair the viability of pups during nursing, pup weight at weaning was reduced in the middle and high dose groups by approximately 12 and 50%, respectively.

Because of the reduced litter size seen during Task 2, a crossover mating trial was conducted using control and high dose animals. During this one-litter trial, there were no differences between control × control pairs and those containing an NF-treated partner. Thus, an affected gender was not identified.

After this trial, the F_0 adults from all treatment groups were killed and necropsied. High dose NF females weighed approximately 5% less than their controls, while their adjusted kidney weight was increased by approximately 11%. There were no differences in antemortem estrous cycle characteristics. Histologically, there was a slight increase in hepatitis in the treated females, but no other remarkable lesions. In males, body weight was unaffected, while adjusted kidney weight was increased (10%) at the high dose. There were no changes in sperm parameters and no significant microscopic lesions.

Mice from the control, middle, and high dose groups were evaluated in the second generation. Only 33% of cohabited females in the high dose delivered a litter, compared to 19 of 20 controls. The high dose group delivered 26% fewer pups per litter, although pup viability and weight were unaffected.

After the F_2 pups were delivered and evaluated, the F_1 adults were killed and the control and high dose mice were necropsied. High dose females weighed 12% less than controls, while adjusted kidney weight was increased by 7%. Antemortem estrous cycle length was unchanged by NF consumption, and no significant microscopic lesions were found. For high dose males, body weight was reduced by 8%, and absolute testis weight was 23% less than controls. Adjusted kidney weight was 13% greater, while adjusted epididymis weight as reduced by 15%. Epididymal sperm density was reduced by approximately 50%, and sperm motility was reduced by approximately 25%. Microscopically, there was a significant increase, at the high dose, in seminiferous tubule degeneration, interstitial cell hyperplasia, and immature germ cells in epididymal lumina. There were no remarkable hepatic or renal lesions.

Thus, in both generations, nitrofurantoin consumption by mice reduced litter size at the high dose, the same level that increased kidney weight. NF had adverse effects on the preweaning growth of the second generation. The second-generation males showed a greater effect on sperm indices than was seen in the first generation, though this might plausibly be related to the preweaning growth-retarding effects of NF. Further work is needed to assess this possible relationship.

Summary: NTP Reproductive Assessment by Continuous Breeding Study.

NTIS#: **PB93175354**
Chemical: **Nitrofurantoin**
CAS#: **67-20-9**
Mode of exposure: **Feed**
Species/strain: **Swiss CD-1 mice**

F_0 generation — Dose concentration →	0.03%	0.06%	0.12%
General toxicity	Male, female	Male, female	Male, female
Body weight	— , —	— , —	— , ↓
Kidney weight[a]	— , —	— , —	↑ , ↑
Liver weight[a]	— , —	— , —	— , —
Mortality	— , —	— , —	— , —
Feed consumption	— , —	— , —	↓ , ↓
Water consumption	•	•	•
Clinical signs	— , —	— , —	— , —
Reproductive toxicity			
x̄ litters/pair	—	—	—
# live pups/litter; pup wt./litter	— , —	— , —	↓ , —
Cumulative days to litter	—	—	—
Absolute testis, epididymis weight[a]	— , —	— , —	— , —
Sex accessory gland weight[a] (prostate, seminal vesicle)	— , —	— , —	— , —
Epidid. sperm parameters (#, motility, morphology)	— , — , —	— , — , —	— , — , —
Estrous cycle length	—	—	—

Determination of affected sex (crossover)	Male	Female	Both
Dose level	—	—	—

F_1 generation — Dose concentration →	•	0.06%	0.12%
General toxicity	Male, female	Male, female	Male, female
Pup growth to weaning	— , —	↓ , ↓	↓ , ↓
Mortality	— , —	— , —	— , —
Adult body weight	•	— , —	↓ , ↓
Kidney weight[a]	•	— , •	↑ , ↑
Liver weight[a]	•	— , •	— , —
Feed consumption	•	— , —	— , —
Water consumption	•	•	•
Clinical signs	— , —	— , —	— , —
Reproductive toxicity			
Fertility index	•	—	↓
# live pups/litter; pup wt./litter	•	— , —	↓ , —
Absolute testis, epididymis weight[a]	•	— , —	↓ , ↓
Sex accessory gland weight[a] (prostate, seminal vesicle)	•	— , —	— , —
Epidid. sperm parameters (#, motility, morphology)	•	— , —	↓ , ↓ , —
Estrous cycle length	•	•	—

Summary information	
Affected sex?	Unclear
Study confounders:	None
NOAEL reproductive toxicity:	0.06%
NOAEL general toxicity:	0.03%
F_1 more sensitive than F_0?	Yes
Postnatal toxicity:	Yes

Legend: —, no change; •, no observation; ↑ or ↓, statistically significant change ($p<0.05$); — , —, no change in males or females. [a]Adjusted for body weight.